## REMARKS

This responds to the Office Action mailed on October 9, 2007, and the references cited therewith.

Claim 18 is cancelled without prejudice to its prosecution in another application. Claims 1-3, 5-10, 12-17 and 20-22 are now pending in this application.

Applicant submits that no new matter has been added to the application.

### *§112, First Paragraph, Rejection of the Claims*

Claims 1-3, 5-10, 12-18 and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In his response to Applicants arguments, the Examiner alleges the specification fails to enable: (1) all HIV Gag, Gp120, Nef or Pol peptides; (2) an immunoprotective response; and (3) all recombinant pox viruses.

**Peptides**

The Examiner alleges that not all HIV Gag, Gp120, Nef or Pol peptides are enabled by the specification.

Applicant submits that the specification fully enables one of skill in the art to make and use the invention, as evidenced not only by the results in the application, and those previously made of record, but also by various articles published after the filing date of the application.

For example, Dorrell et al., (J. Virol. 80: 4705-16 (2006); provided in the January 7, 2008 Supplemental Information Disclosure Statement (SIDS)), provides data on HIV infected patients who had received highly active antiretroviral therapy (HAART), and were then administered a modified vaccinia virus Ankara (MVA) that expresses an immunogen, HIVA, which includes consensus HIV-1 Gag p24/p17 sequences. Those patients exhibited CD8+ T cell responses against at least 8-10 peptides that were previously undefined as HIV epitopes (see Table 2 and page 4709, left column). Moreover Dorrell reports that tetramer staining revealed long-lived vaccine-driven CD8+ T-cell expansions, and that CD8+ and CD4+ T-cell proliferative responses to HIV-1 Gag were enhanced by administration of this recombinant MVA pox virus (page 4709).

Moreover, Tubiana et al. (Vaccine 23:4292-4301 (2005); also provided in the January 7, 2008 SIDS) provides additional results for HAART-treated patients who were administered an ALVAC-HIV vCP 1433, which is a recombinant canarypox virus expressing the products of several HIV genes: a part of *env* expressing the glycoprotein gp120 (MN strain) and the anchoring region of gp41 (LAI strain), *gag* with the p24 protein (LAI strain), protease expressing the p15 protein (LAI strain), and several immunodominant CTL epitopes from the *nef* and *pol* gene products (see page 4294). As explained by Tubiana, during the immunization phase, increases in CD8 responses were observed in 11 patients (55%) and included at least a threefold amplification from baseline of HIV-gag-specific CD8 T cell numbers ($n = 3$ patients), or a diversification of these responses, as defined by at least one novel gag-peptide pool recognized ($n = 3$ patients), or both a threefold amplification and a diversification ($n = 5$ patients) (see, Tubiana Fig. 3 and page 4297, left column).

Thus, the method of the invention, which includes treatment with one or more anti-viral agents, which contributed to a lower viral copy and higher $CD4^+$ cell count, followed by administration of an attenuated recombinant pox virus, stimulates a HIV1-specific $CD8^+$ response in a human infected with an HIV retrovirus. And as shown by Dorrell and Tubiana, the CD8+ response can *diversify* to HIV peptide epitopes that were not previously recognized by the patients immune system. These data therefore show that a variety of HIV peptides can successfully be used in the methods of the invention.

Accordingly, the methods of the invention do enable use of a variety of peptides. Applicant respectfully requests withdrawal of this rejection.

**Protective Immune Response**

The Examiner interprets the claims to encompass therapeutic vaccine responses and then states that vaccine development is characterized by unpredictability.

Applicant reminds the Examiner that the claims are not drawn to vaccines and methods of providing protective immunity against viral infection. Instead, the claims are drawn to methods of stimulating a HIV1-specific $CD8^+$ response in humans/mammals already infected with an HIV.

Applicant submits that the Examiner is reading language from the specification into the claims, contrary to the dictates of patent law. Because the claims do not call for vaccines and do not require protection against or prevention of HIV-infection, it is irrelevant whether or not currently available vaccines are actually effective at preventing HIV infection.

Moreover, Applicant has provided several examples showing that the present methods do stimulate a HIV1-specific $CD8^+$ response in humans/mammals already infected with an HIV.

With this response, Applicant has provided the articles of Dorrell and Tubiana (cited above) both showing that the present methods stimulate a CD8+ response. In particular, Dorrell shows that methods employing the MVA.HIVA pox virus stimulated proliferation of both CD4+ and CD8+ T cells in 75% of patients (see 4714, right column, first complete paragraph). Dorrell further demonstrates that MVA.HIVA administration increased not only the magnitude of CD4+ and CD8+ T-cell responses but also the breadth of these responses, with targeting of CD8+ T-cell epitopes in Nef, Pol, and Env proteins which were expressed in the epitope string, together with conserved regions of the Gag protein, and of previously unrecognized Gag epitopes (page 4714, left column, first complete paragraph). Dorrell concludes that, using the methods described therein, it is possible to boost responses to subdominant T-cell epitopes (i.e., peptides other than those previously identified to be good T-cell epitopes).

In addition, Applicants have provided a Declaration by Dr. Genoveffa Franchini (in May 2005) that describes two clinical trials conducted by Aventis Pasteur as well as proposed clinical trials by EuroVacc. The clinical trials involved administration of a recombinant pox virus that encoded HIV peptides (vCP1452) to human HIV-infected patients. In the ACTG5054 Trial, the patients had been undergoing antiretroviral therapy (ART) and prior to administration of vCP1452 had a median CD4 count of 609 and a viral load of less than 50 (see pages 3 and 5 of the Declaration Appendix). Preliminary results indicate that patients who received the recombinant vCP1452 pox virus alone had a lower viral load than those who received placebo (page 5 of the Declaration Appendix)). In the Quest trial, patients who received the recombinant pox virus had

increased CD4+ and CD8+ responses at week 24 (see page 11 of the Declaration Appendix). The results of the Quest trial with respect to increased CD4+ and CD8+ responses were confirmed by a more complete study as shown in Kimloch-de Loes et al., J. Infect. Diseases 192: 607-17 (2005) (provided in the January 7, 2008 SIDS).

Applicants have previously submitted an article by Jin et al. (J. Virol. 76: 2206-16 (2002)), which shows that administration of the ALVAC vCP1452 recombinant virus stimulates an HIV1-specific $CD8^+$ response in HIV-infected patients who have been receiving antiretroviral therapy. Patients included in this study were infected with HIV but had a viral load of 50 copies HIV-1 RNA per ml plasma and an average CD4 count of 779 (see page 2207). As stated at page 2211 of the Jin et al. article, 78% of patients had an increase in $CD8^+$ T-cell responses to at least one HIV-1 antigen (see also Figure 4b and pages 2213-14). The recombinant vCP1452 virus is a recombinant pox virus that encoded gp120, gp41, p55, pol and nef HIV peptides (*id.* at page 2207).

Therefore, the claims are not drawn to prevention of HIV infection and the teachings of the specification have been confirmed by results obtained since the filing data of the application. Applicant respectfully requests withdrawal of this rejection.

**Pox Viruses**

The Examiner states that while Applicants have provided preliminary results on use of ALVAC recombinant pox viruses encoding Gag, PR and Env and have observed a reduced viral load in that study, but that the claims are not directed to any particular expression vector or HIV/retroviral epitope.

Applicant submits that any type of recombinant pox virus can be used in the invention. This is demonstrated by the results obtained by Applicants with ALVAC and NYVAC recombinant pox viruses, by Tubiana with other ALVAC recombinant pox viruses, as well as by Dorrell with MVA recombinant pox viruses.

Therefore, different types of recombinant pox viruses can be used in the methods of the invention. Applicant submits that the invention is fully enabled with respect to recombinant pox viruses. Applicant respectfully requests withdrawal of this rejection.

The Examiner has also repeated argumentation that the specification fails to provide adequate guidance with respect to the following considerations.

**Immunogens for inducing a therapeutic HIV-specific CD8+ immune response**

The Examiner has alleged that the specification does not enable immunogens capable of inducing a therapeutic HIV-specific CD8+ immune response.

However, the claims are directed to specific immunogens -- HIV specific peptides including HIV Gag, Gp120, Env, Nef or Pol peptides. As described in the specification at page 18, line 24 to page 21, line 28, and shown in FIG. 2, anti-viral agent treated animals who were inoculated with a recombinant NYVAC that produces gag-pol-env HIV specific peptides (Group B), exhibited substantially increased percentages of HIV-specific $CD8^+$ T cells relative to anti-viral agent treated animals that received a placebo vaccine (Group A) or animals inoculated with the recombinant NYVAC virus who had received no anti-viral agent treatment (Group C).

The work of Dorrell and Tubiana (cited above) confirm that the present methods stimulate a CD8+ response. Thus, Dorrell demonstrates that the breadth of the CD8+ response is improved so that previously unrecognized Gag epitopes are also recognized by T cells (page 4714, left column, first complete paragraph). Dorrell concludes that, using the methods described therein, it is possible to boost responses to subdominant T-cell epitopes (i.e., peptides other than those previously identified to be good T-cell epitopes). Similarly, Tubiana shows that the CD8+ response can *diversify* to HIV peptide epitopes that were not previously recognized by the patients immune system. These data therefore show that a variety of HIV peptides can successfully be used in the methods of the invention.

Thus, the specification clearly does enable a variety of immunogens capable of inducing therapeutic HIV-specific CD8+ immune response. Applicant respectfully requests withdrawal of this rejection.

**Guidance as to the correlates of human protection**

The Examiner asserts that the specification does not provide guidance on the correlates of human protection and states that the specification fails to address the suggested need for both polyfunctional (IL-2 and IFN-γ) CD4+ and viral-specific CD8+ T-cell responses. The Examiner again argues that CD8+ T-cell responses cannot prevent infection.

However, the method of the invention are drawn to stimulating a HIV1-specific $CD8^+$ response in HIV-infected patients and not to preventing HIV infection in patients. Applicant reminds the Examiner that the terms "protection" and "prevention" are not used in the claims.

Moreover, the Examiner's allegations that the specification fails to enable CD4+ as well as CD8+ responses are induced by the present methods is untrue. In fact, the specification provides data (FIG. 1) showing that gp120-specific CD4+ T cell proliferation was significantly increased in animals that received both anti-retroviral agents and the recombinant NYVAC virus that produces gag-pol-env HIV specific peptides (Group B). The application further discloses that proliferative CD4+ responses to p27 Gag and gp120 were increased by NYVAC gag-pol-env vaccination up to three- and twelve-fold (page 25, lines 11-15). Thus, the specification teaches one of skill how to generate CD4+ as well as CD8+ responses.

Similarly, both Dorrell and Tubiana confirm the teachings of Applicant's specification. In particular, Dorrell provides data showing that a recombinant MVA vaccine, administered during HAART, efficiently expands both CD8+ and CD4+ T cells with a favorable functional profile for containing virus replication (see, e.g., sentence bridging pages 4714-4715). Tubiana also provides data showing that both HIV-specific CD4 and CD8 T cell responses were boosted (in about 50% patients, see, e.g., page 4298, in the paragraph under "Discussion"). Thus, articles published after the filing date of the application confirm the teachings of the application that the methods of the invention stimulate both CD4+ and CD8+ responses.

Applicant respectfully requests withdrawal of this rejection.

**Quasispecies nature of HIV**

The Examiner alleges that the HIV-1 genome is plastic and contributes to immune escape, asserting that the specification fails to provide guidance concerning the identification of epitopes that are resistant to viral escape.

Applicant submits that the invention is drawn to a use of variety of epitopes (not one single antigenic peptide) to optimally stimulate the immune system against a variety of viral antigens and thereby minimize the probability of escape. As the specification discloses, "Following therapy suspension, NYVAC-SIV-vaccinated animals were able to control viremia better than animals treated with antiretroviral therapy alone." The present methods are clearly therapeutically beneficial, as confirmed by the Dorrell and Tubiana publications.

Applicant respectfully requests withdrawal of this rejection.

**Working Examples**

The Examiner asserts that the only examples provided in the specification are prophetic.

However, the specification provides data (FIG. 2, page 18, line 24 to page 21, line 28) showing that HAART-treated animals who were inoculated with a recombinant NYVAC, which produces gag-pol-env HIV specific peptides (Group B), exhibited substantially increased percentages of HIV-specific $CD8^+$ T cells relative to HAART-treated animals who received a placebo vaccine (Group A) or animals inoculated with the recombinant NYVAC virus who had received no HAART treatment (Group C). Thus, as the specification discloses at page 22, lines 8-10, the inventive methods induced significant expansion of the number of CD8+/CD3+ cells specific for an immunodominant gag peptide only in animals treated effectively with antiretroviral therapy (i.e., both anti-retroviral agents and the recombinant NYVAC virus that produces gag-pol-env HIV specific peptides).

Applicant submits that the results of these Examples and the teachings of the application have been confirmed in human patients as shown by the Franchini Declaration, and the Tubiana, Kimloch-de Loes and Dorrell publications.

Applicant respectfully requests withdrawal of this rejection.

**State of the art**

The Examiner asserts that not one single effective HIV CTL vaccine is on the market and undue experimentation would be required to identify vaccines that would have long-lasting and high titer immune responses.

Applicant reminds the Examiner that the term "vaccine" is not present in the claims. Hence, the failure of others to produce a protective/preventive vaccine is irrelevant to present application.

Moreover, it is in the nature of an invention to move the state of the art forward, beyond what was predictable prior to the filing date of the application. Applicant appreciates the Examiner's comments that the present invention is distinct from the prior art.

Finally, the results of practicing the invention (stimulation of a CD8+ response) have been demonstrated in at least three instances since the application was filed.

For example, Dorrell et al., (J. Virol. 80: 4705-16 (2006)), provides data on HIV infected patients who had received highly active antiretroviral therapy (HAART), and were then administered a modified vaccinia virus Ankara (MVA) that expresses an immunogen, HIVA, which includes consensus HIV-1 Gag p24/p17 sequences. Those patients exhibited CD8+ T cell responses against at least 8-10 peptides that were previously undefined as HIV epitopes (see Table 2 and page 4709, left column). Moreover Dorrell reports that tetramer staining revealed long-lived vaccine-driven CD8+ T-cell expansions, and that CD8+ and CD4+ T-cell proliferative responses to HIV-1 Gag were enhanced by administration of this recombinant MVA pox virus (page 4709).

Second, the results of the Quest trial with respect to increased CD4+ and CD8+ responses were confirmed by a more complete study as shown in Kimloch-de Loes et al., J. Infect. Diseases 192: 607-17 (2005).

Third, Tubiana et al. (Vaccine 23:4292-4301 (2005)) shows that HAART-treated patients who were administered an ALVAC-HIV vCP 1433, expressing part of *env*, *gag*, protease, *nef* and *pol* gene products (see page 4294) exhibited increased CD8 responses in

55% of patients tested. Several patients exhibited at least a threefold amplification from baseline of HIV-gag-specific CD8 T cell numbers ($n = 3$ patients), or a diversification of these responses, as defined by at least one novel gag-peptide pool recognized ($n = 3$ patients), or both a threefold amplification and a diversification ($n = 5$ patients) (see, Tubiana Fig. 3 and page 4297, left column).

Therefore, ample evidence exists demonstrating that the methods of the invention can readily be practiced by one of skill in the art to stimulate a CD8+ response in HIV-infected patients.

Applicant respectfully requests withdrawal of this rejection.

## CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

GENOVEFFA FRANCHINI ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(516) 795-6820

Date January 9, 2008

By /Robin A. Chadwick/
Robin A. Chadwick
Reg. No. 36,477

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 9th day of January, 2008.

Dawn M. Poole

Name

Signature